REMARKS

Amendments

The above-captioned application incorporates by reference the entire contents of United States Patent Nos. 5,500,412 and 5,352,664 (see specification as submitted 09/909,122 at page 5, line 3).

In this amendment, the specification has been amended to include a two-paragraph portion of the material previously incorporated by reference from those patents. The one-paragraph portion is identically recited in both patents and is contained at column 6, lines 35-49 of United States Patent No. 5,500,412 and from column 6, line 54 to column 7, line 2 of United States Patent No. 5,352,664.

The paragraphs were added by amendment to the application as submitted July 19, 2001, on page 6, between paragraph 1 and paragraph 2, at line 16, and are directed to, for example, physiologically functional equivalents of thrombin derivatives which encompass modifications such as amidation of the carboxyl terminus. The term "thrombin derivatives", utilized in United States Patent Nos. 5,500,412 and 5,352,664 has been further clarified in this application to be "thrombin peptide derivatives" for consistency. The present application additionally teaches specific amino acid sequences of thrombin peptide derivatives, such as SEQ ID: NO. 5 (page 7, lines 8-10).

The present application has been further amended at page 3, line 14 and at page 7, lines 19-20, to place the teachings directed to the physiologically functional equivalents of thrombin peptide derivatives as described in the preceding paragraph in additional locations in the present application. The purpose of these amendments is to more readily convey this aspect of the invention to the public. Further to that end, the amino acid sequence of SEQ ID: NO. 5, the thrombin peptide derivative, has been additionally represented as a sequence with an amide at the C-terminus in SEQ ID: NO. 6, a physiologically functional equivalent of a thrombin peptide derivative.

The subject matter of new Claims 38-43 is fully supported in the present application as filed July 19, 2001. Support can be found at least in the two paragraphs added from United States Patent Nos. 5,352,664 and 5,500,412 and in the subject application at page 7, lines 8-10.

A number of claims have been amended to replace the terms "has" and "having" with "consists of" and "consisting of", respectively. Applicants view the language "has" and "having" in this context as being synonymous with "consists of" and "consisting of", respectively. These changes are intended to make the language of the claims more consistent and definite, and do not narrow the original scope of the claims so amended.

No new matter has been added by the amendments to the specification or by the new claims. Therefore, their entry into the present application is respectfully requested.

Response to Restriction Requirement

Responsive to the Restriction Requirement dated September 30, 2002, the claims of Group 1, drawn to a method of stimulating bone growth at a site in a subject, are elected for prosecution. The claims of Group 1 include Claims 1-16 and 35-37, as amended, and, it is believed, new claims 38-43. Applicant reserves the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicant does not hereby abandon or waive any rights in the non-elected inventions.

Responsive to the requirement for an election of species and a species variant for searching purposes, Applicant hereby elects SEQ ID: NO. 6 (Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2) in the amended sequence listing as the species and species variant. Claims readable on the elected species include Claims 1-16 and 35-37, as amended, and, it is believed, new claims 38-43.

CONCLUSION

Claims 1-43 are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

In the application as submitted July 19, 2001, please replace paragraph 2 at page 2, lines 12-21, with the following paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

(Amended) Compounds which stimulate or induce bone growth at sites where such growth would not normally occur if left untreated are said to be "osteoinductive". An osteoinductive compound would have great value as a drug to treat the conditions described above. A number of osteoinductive proteins have been identified, isolated and expressed using recombinant technology. Examples include the bone morphogenic proteins (BMPs) disclosed in U.S Patent No. 5,902,705 and[in] WO 95/16035. However, the use of recombinant proteins as therapeutic agents generally has a number of drawbacks, including the cost of manufacture, *in vivo* biodegradation and short shelf lives. Consequently, scientists are continuing to search for new osteoinductive agents which do not have the aforementioned shortcomings.

In the application as submitted July 19, 2001, please replace paragraph 3 on page 3, lines 10-17, with the following paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

(Amended) The method of the present invention is directed at stimulating bone growth in a subject and can be used at sites where bone growth would not occur, absent treatment with autologous bone grafts or administration of bone growth factors. The method involves the administration of agonists of the non-proteolytic thrombin receptor. Such agonists include small peptides, and physiologically functional equivalents, having homology to the segment between

amino acid 508 and 530 of human prothrombin. These small peptides are inexpensive to prepare in bulk quantities and are osteoinductive at low dose. In addition, their lyophilized form is stable for at least thirty months when stored at 5° C and at 60% relative humidity.

In the application as submitted July 19, 2001, please replace paragraph 2 on page 7, lines 19-20 with the following paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

(Amended) TP508 is an example of a thrombin peptide derivative and has the amino acid sequence of SEQ ID: NO. 5. A physiologically functional equivalent of SEQ ID: NO. 5 is SEQ ID: NO. 6 which has the identical amino sequence of SEQ ID: NO. 5 and also contains a C-terminal amide.

In the application as submitted July 19, 2001, at page 6, between paragraph 1 and paragraph 2, at line 16, add the following new paragraphs.

(New) A physiologically functional equivalent of a thrombin peptide derivative encompasses molecules which differ from thrombin peptide derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences.

(New) A thrombin receptor binding domain is defined as a polypeptide sequence which directly binds to the thrombin receptor and/or competitively inhibits binding between high-affinity thrombin receptors and alpha-thrombin.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

4. (Amended) ~~The method of Claim 1 wherein~~ the agonist is a thrombin peptide derivative, or a physiologically functional equivalent thereof, comprising a polypeptide represented by the following ~~structural formula~~:

Asp-Ala-R;

wherein R is a serine esterase conserved sequence.

5. (Amended) The method of Claim 4 wherein the agonist[thrombin peptide derivative] consists of[has] between about 12 and about 23 amino acids.

6. (Amended) The method of Claim 5 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a C-terminal truncated fragment thereof consisting of[having] at least six amino acids, provided that zero, one, two or three amino acids in the serine esterase conserved sequence differ from the corresponding position of SEQ ID: NO. 1.

7. (Amended) The method of Claim 5 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a C-terminal truncated fragment thereof consisting of[having] at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved region are conservative substitutions[susbstitutions] of the corresponding amino acid in SEQ ID: NO. 1.

8. (Amended) The method of Claim 5 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 2 (Cys-X1-Gly-Asp-Ser-Gly-Gly-Pro-X2-Val, wherein X1 is Glu or Gln and X2 is Phe, Met,

Leu, His or Val), or a C-terminus truncated fragment of SEQ ID: NO. 2, said fragment consisting of[having] at least six amino acids.

9. (Amended) The method of Claim 8 wherein the agonist[thrombin peptide derivative] comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID: NO. 3).

10. (Amended) The method of Claim 9 wherein the agonist[thrombin peptide derivative] comprises the amino acid sequence Arg-Gly-Asp-Ala-Cys-X1-Gly-Asp-Ser-Gly-Gly-Pro-X2-Val (SEQ ID: NO. 4), wherein X1 is Glu or Gln and X2 is Phe, Met, Leu, His or Val.

11. (Amended) The method of Claim 10 wherein the agonist[thrombin peptide derivative] consists of[has] the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID: NO. 5), or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the agonist[thrombin peptide derivative] differ from the amino acid at the corresponding position of SEQ ID: NO. 5.

12. (Amended) The method of Claim 10 wherein the agonist[thrombin peptide derivative] consists of[has] the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID: NO. 5), or an N-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the agonist[thrombin peptide derivative] are conservative substitutions of the amino acid at the corresponding position of SEQ ID: NO. 5.

13. (Amended) The method of Claim 11 wherein the agonist[thrombin peptide derivative] is administered in a pharmaceutical composition additionally comprising an implantable, biocompatible carrier.

19. (Amended) The pharmaceutical composition of Claim 18, wherein the thrombin receptor agonist is a thrombin peptide derivative, or a physiologically functional equivalent thereof, comprising[comprises] a polypeptide represented by the following structural formula:

Asp-Ala-R;

wherein R is a serine esterase conserved sequence.

27. (Amended) The pharmaceutical composition of Claim 19 wherein the agonist[thrombin peptide derivative] consists of[has] between about 12 and about 23 amino acids.

28. (Amended) The pharmaceutical composition of Claim 27 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a ~~C~~-terminal truncated fragment thereof consisting of[having] at least six amino acids, provided that zero, one, two or three amino acids in the serine esterase conserved sequence differ from the corresponding position of SEQ ID: NO. 1.

29. (Amended) The pharmaceutical composition of Claim 27 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a C-terminal truncated fragment thereof consisting of[having] at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved sequence are conservative substitutions[susbstitutions] of the corresponding amino acid in SEQ ID: NO. 1.

30. (Amended) The pharmaceutical composition of Claim 27 wherein the serine esterase conserved sequence consists of[has] the amino acid sequence of SEQ ID: NO. 2 (Cys-X1-Gly-Asp-Ser-Gly-Gly-Pro-X2-Val) , wherein X1 is Glu or Gln and X2 is Phe, Met, Leu, His or Val), or a C-terminus truncated fragment of SEQ ID: NO. 2, said fragment consisting of[having] at least six amino acids.

31. (Amended) The pharmaceutical composition of Claim 30 wherein the agonist[thrombin peptide derivative] comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID: NO. 3).

32. (Amended) The pharmaceutical composition of Claim 31 wherein the agonist[thrombin peptide derivative] comprises the amino acid sequence Arg-Gly-Asp-Ala-Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val (SEQ ID: NO. 4), wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val.

33. (Amended) The pharmaceutical composition of Claim 32 wherein the agonist[thrombin peptide derivative] consists of[has] the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID: NO. 5), or an N-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the agonist[thrombin peptide derivative] differ from the amino acid at the corresponding position of SEQ ID: NO. 5.

34. (Amended) The pharmaceutical composition of Claim 32 wherein the agonist[thrombin peptide derivative] consists of[has] the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID: NO. 5), or an N-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the agonist[thrombin peptide derivative] are

conservative substitutions of the amino acid at the corresponding position of SEQ ID: NO. 5.

35. (Amended) A method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of a peptide consisting of[having] the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID: NO. 5).

36. (Amended) A method of stimulating bone growth at a site in need of a bone graft in a subject, said method comprising the step of administering to the site a therapeutically effective amount of a peptide consisting of[having] the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID: NO. 5).

37. (Amended) A method of stimulating bone growth in a subject at a segmental bone gap, a bone void or a non-union fracture[facture], said method comprising the step of administering to the bone gap, bone void or nonunion fracture[facture] a therapeutically effective amount of a peptide consisting of[having] the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID: NO. 5).

38. (New) The method of Claim 5, wherein the agonist comprises a C-terminal amide.

39. (New) The method of Claim 5, wherein the agonist comprises Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID: NO. 6).

40. (New) The method of Claim 5, wherein the agonist consists of Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID: NO. 6).

41. (New) A method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist consisting of the sequence of Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID: NO. 6).

42. (New) A method of stimulating bone growth at a site in need of a bone graft in a subject, said method comprising the step of administering to the site a therapeutically effective amount of an agonist consisting of the sequence of Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID: NO. 6).

43. (New) A method of stimulating bone growth at a segmental bone gap, a bone void or a non-union fracture, said method comprising the step of administering to the bone gap, bone void or non-union fracture a therapeutically effective amount of an agonist consisting of the sequence of Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID: NO. 6).